Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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P. M. Veeresha Sharma [a] & M. G. Purohit [b]

[a] Department of Organic Chemistry, Indian Institute of Science, Bangalore, India

[b] Department of Chemistry, Gulbarga University, Gulbarga, India

Published online: 25 Apr 2008.

To cite this article: P. M. Veeresha Sharma & M. G. Purohit (2008): Novel Synthesis of 5-Substituted-3-phenylindole-2-(1,2,4-triazole) Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 38:9, 1381-1388

To link to this article: http://dx.doi.org/10.1080/00397910801914160

Synthetic Communications®, 38: 1381–1388, 2008

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910801914160

Novel Synthesis of 5-Substituted-3-phenylindole-2-(1,2,4-triazole) Derivatives

P. M. Veeresha Sharma[1] and M. G. Purohit[2]

[1]Department of Organic Chemistry, Indian Institute of Science, Bangalore, India
[2]Department of Chemistry, Gulbarga University, Gulbarga, India

Abstract: Various substituted 3-phenylindole 2-carboxylates **(1a–c)** were prepared according to the literature methods. These carboxylates **(1a–c)** on reaction with thiosemicarbazide yielded 5-substituted-3-phenylindol-2-(1,2,4-triazole-3-thione) **(2a–c)** on refluxing in pyridine for 8 h. The 5-substituted-3-phenylindole-2-[1,2,4-triazolo-3-thioacetic acid] **(3a–c)** were prepared from 5-substituted-3-phenyl indole-2-[1,2,4-triazole-3-thione] **(2a–c)** on reaction with an appropriate alkylating agent and sodium acetate in acetic acid. Further, **(3a–c)** were reacted with acetic anhydride to bring about a cyclocondensation reaction to yield 5-substituted-3-phenylindol-2-thiazolo(2,3-b)-triazole **(4a–c)**. The 5-substituted-3-phenylindole-2-[1,2,4-triazolo-3-acetic acid] **(3a–c)** were reacted with o-phenylenediamino dihydrochloride in ethylene glycol to yield 5-substituted-3-phenylindole-1,2,4-triazolo-3′-yl-thiomethyl)benzimidazoles **(5a–c)**.

Keywords: 3-Phenylindole-2-carboxylates, thiosemicarbazides, alkylating agents, cyclocondensation

INTRODUCTION

A literature survey reveals that indole and its derivatives represent one of the most pharmcologically active classes of compounds. Still, there is an immense research interest in preparing indole derivatives because of their efficient use in anti-HIV activity and varied biodynamic properties. The indole nucleus is present in number of physiologically significant

Received October 11, 2007
Address correspondence to M. G. Purohit, Department of Chemistry, Gulbarga University, Gulbarga 585106, India. E-mail: murleedhar_purohit@hotmail.com

compounds. For example, indole-3-acetic acid (heteroauxin) is a naturally occurring plant growth hormone. Tryptophan is a naturally occurring essential amino acid, which plays a vital role in the biosynthesis of cellular proteins and porphyrins in animals. Reserpine is an indole alkaloid that reduces the concentration of serotonin in central nervous tissue. In recent years, there are increasing numbers of reports on the synthesis of indole analogs for their agrochemical anthelmintic activity and also COX-II enzyme inhibitory activity.[1,2]

The triazoles also exhibit broad-spectrum pesticidal activities. Certain heterocyclic compounds with a 1,2,4-triazole nucleus are reported to possess fungicidal, insecticidal, and antimicrobial activities. Some of the triazole derivatives have been synthesized for possible anticonvulsants, antidepressant plant growth hormone, and antitubercular molecules.[3,4]

A literature survey reveals that benzimidazole and its derivatives possess diverse pharmacological properties such as analgesic, anti-inflammatory, tranquilizing anticonvulsant, and central nervous system (CNS) inhibition activity.[5]

In this article, we report the novel preparation and characterization of 5-substituted-3-phenylindole-2-(1,2,4-triazole) derivatives.

RESULTS AND DISCUSSION

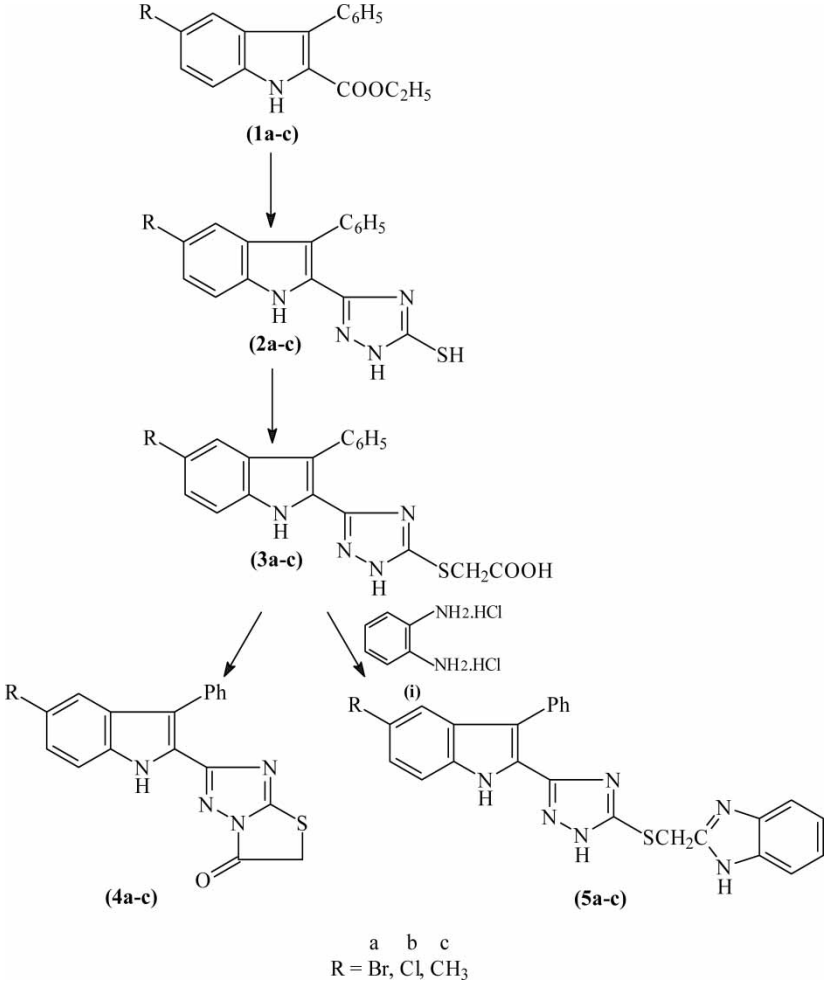
On reaction with thiosemicarbazide, the indole-2-carboxylates (**1a**–**c**) yielded 5-substituted-3-phenylindol-2-(1,2,4-triazole-3-thione) (**2a**–**c**). The formation of these compounds was confirmed by their IR, NMR, and mass spectral data. The IR spectrum of **2a** displayed an absorption peak at 3328 cm^{-1} as a result of NH of indole. Another peak at 3280 cm^{-1} can be assigned for triazole NH. The ^1H NMR spectrum of **2a** exhibits a sharp singlet downfield at 9.2 ppm because of the resonance of H of indole NH. Another singlet at 8.6 ppm may be due to the proton of SH group. A single proton present on the triazole moiety has shown a peak at 7.8 ppm. The multiplet from 7.2 to 7.6 ppm is expected to be due to the protons of aromatic region.

These spectral data of **2a** described previously confirms the structure assigned to **2a** obtained by the reaction of **1a** with thiosemicarbazide in pyridine. Other compounds (**2b** and **2c**) also exhibit the spectral properties as per the discussion mentioned before. Hence, the structure assigned to **2a**–**c** obtained by the reaction with **1a**–**c** is in conformity with the expected structure.

The 5-substituted-3-phenylindole-2-[1,2,4-triazolo-3-thioacetic acid] (**3a**–**c**) were prepared from 5-substituted-3-phenylindole-2-[1,2,4-triazole-3-thione] (**2a**–**c**) with an appropriate alkylating agent and sodium acetate in acetic acid. The structures of **3a**–**c** were confirmed by their spectral data. The IR spectrum of **3a** exhibits absorption peaks at 3312, 2987, and 1682 cm^{-1}, attributable to NH/NH, C═O, and functional groups present in

the molecule. ^{1}H NMR of **3b** shows a peak at 10.0 ppm for H of COOH. Another peak at 9.1 ppm was attributed to H of indole NH and a singlet peak at 7.8 ppm to triazole NH. The multiplet from 7.3 to 7.6 ppm is for the protons of aromatic ring. The peak at 4.3 ppm is due to -CH_2 protons as a singlet. The other compounds (**3b** and **3c**) exhibit identical spectral data with respect to **3a**. Hence, structures assigned to **3a**–**c** are in conformity with the proposed structures.

Further **3a**–**c** was reacted with acetic anhydride to bring about a cyclo-condensation reaction to yield 5-substituted-3-phenylindol-2-thiazolo (2,3-b) triazole (**4a**–**c**). The IR spectrum of **4a** displays absorption peaks at



Scheme 1.

3311 cm^{-1} for indole NH functional group, and at 1685 cm^{-1} for cyclic C═O group. ^1H NMR spectrum of **4a** exhibits a peak at 12.1 ppm for H of indole NH. The peak due to H of triazole NH appeared in the precursor has disappeared in the spectrum of **4a**. This observation supports the cyclization to yield expected compound **5**. Two protons of the thiazole ring appear as a singlet at 4.2 ppm. The aromatic protons appear as a multiplet from 7.3 to 7.6 ppm (Scheme 1).

These spectral data of **4a** confirm the structures of **4a–c** from **3a–c**. All other compounds (**4a–c)** exhibit identical spectral data with respect to **4a**. The 5-substituted-3-phenylindole-2-[1,2,4-triazolo-3-acetic acid] (**3a–c)** was reacted with O-phenylenediamino dihydrochloride in ethylene glycol to yield 5-substituted-3-phenyl indole-1,2,4-triazolo-3′-yl-thio methyl) benzimidazoles (**5a–c)**. The spectrum of **5b** shows a broad peak at 3313 cm^{-1} for the absorption of NH/NH functionality of indole and triazole. The ^1H NMR spectrum of **5b** exhibits a downfield peak at 9.1 ppm, due to the resonance of H of indole NH. The H of triazole NH appears as a singlet at 7.8 ppm. The multiplet in the region from 7.2 to 7.6 ppm is due to aromatic protons. The protons of $-CH_2$ appear as a singlet at 4.3 ppm. Furthermore, the structure of **5b** is supported by its mass spectra. Other derivatives (**5a–c**) also exhibit identical spectral properties, confirmed by their spectral data (Table 1).

EXPERIMENTAL

Ethyl 3,5-Disubstituted Indole-2-carboxylates (1a–c)

Ethyl α-benzylaceto acetate: Anhydrous ethanol (780 mL) was placed in a three-necked flask (2 L), filled with reflux condenser, mercury-sealed stirrer, and a dropping funnel. Small pieces of sodium (38.8 g, 1.6 mol) were added and dissolved to form sodium ethoxide. Ethylacetoacetate (21 g, 1.6 mol) was added to this with stirring for 2 h, followed by benzyl chloride (208 g, 1.7 mol). The reaction mixture was heated under reflux on a water bath for 4–5 h and kept for 4 h at room temperature. Ethanol was distilled off under reduced pressure, and the residue was diluted with water (1 L). The oil separated after cooling and was extracted with ether. The extract was dried on Na_2SO_4, and the solvent was removed by distillation. Distillation of residual oil under reduced pressure gave ethyl α-benzylacetoacetate as a colorless oil, yield 60%.

Ethyl Phenyl Pyruvate Phenylhydrazones

Ice-cold solution of potassium hydroxide (125 mL, 51%) was added to a vigorously stirred solution of ethyl α-benzyl acetoacetate (82.55 g, 0.375 mol) in

Table 1. Synthesis of some 5-substituted-3-phenylindole-2-(1,2,4-triazole) derivatives

Compound	MP (°C)	Yield (%)	Molecular formula	Found (cald.) C	Found (cald.) H	Found (cald.) N	IR (cm^{-1})	^{1}H NMR (ppm)
2a	162	70	$C_{16}H_{11}N_4SBr$	51.75 (51.62)	2.96 (2.90)	15.00 (15.09)	3328, 3280 NH/NH	9.2 (s, 1H, indole NH), 8.6 (δH), 7.8 (s, triazole NH), 7.2–7.6 (Ar-H)
2b	173	64	$C_{16}H_{11}N_4SCl$	58.80 (58.89)	3.30 (3.37)	17.10 (17.17)	3312 NH, 3260 NH	9.1 (s, 1H, indole NH), 8.7 (stio), 7.6 (s, triazole NH), 7.3–7.8 (Ar-H)
2c	168	68	$C_{17}H_{14}N_4S$	66.65 (66.66)	4.50 (4.57)	18.28 (18.30)	3316, 3260 NH/NH	
3a	148	75	$C_{18}H_{13}N_4O_2SBr$	50.32 (50.34)	3.00 (3.03)	13.00 (13.05)	3312 NH, 1682 (C═O)	9.1 (s, 1H, indole NH), 7.7 (s, triazole NH), 7.3–7.6 (Ar-H)
3b	155	68	$C_{18}H_{13}N_4O_2SCl$	56.20 (56.25)	3.36 (3.38)	14.56 (14.58)	3216 NH, 1690 (C═O)	9.3 (s, 1H, indole NH), 7.5 (s, triazole NH), 7.16–7.5 (Ar-H)
3c	153	76	$C_{19}H_{16}N_4O_2S$	62.60 (62.63)	4.30 (4.39)	15.35 (15.38)	3318 NH, 1659 (C═O)	
4a	180	62	$C_{18}H_{11}N_4SOBr$	52.50 (52.55)	2.60 (2.67)	13.60 (13.62)	3311 (NH), 1685 (C═O)	12.1 (s, 1H, indole NH), 3.3 (triazole CH_2), 7.3–7.6 (Ar-H)

(*continued*)

Table 1. Continued

Compound	MP (°C)	Yield (%)	Molecular formula	Found (cald.) C	Found (cald.) H	Found (cald.) N	IR (cm^{-1})	^1H NMR (ppm)
4b	160	70	$C_{18}H_{11}N_4SOCl$	59.05 (59.01)	3.12 (3.00)	15.32 (15.30)	3317 (NH), 1690 (C═O)	12.2 (s, 1H, indole NH), 3.4 (triazole CH_2), 7.3–7.59 (Ar-H)
4c	166	63	$C_{19}H_{14}N_4SO$	65.85 (65.89)	4.02 (4.04)	16.20 (16.18)	3318 (NH), 1596 (C═O)	
5a	188	56	$C_{24}H_{17}N_6SBr$	57.42 (57.48)	3.35 (3.39)	16.72 (16.76)	3313 (indole NH), 2988 (triazole NH)	9.1 (indole NH), 7.8 (benzimidazole NH)
5b	196	59	$C_{24}H_{17}N_6SCl$	63.14 (63.15)	3.70 (3.72)	18.40 (18.42)	3260 (indole NH), 2860 (triazole NH)	9.36 (indole NH), 7.9 (benzimidazole NH), 7.3–7.8 (Ar-H)
5c	190	60	$C_{25}H_{20}N_6S$	68.50 (68.80)	4.50 (4.58)	19.22 (19.26)	3317 (indole NH), 2890 (triazole NH)	

absolute alcohol (375 mL), maintained at 0 °C, followed by the addition of ice water (700 mL). Immediately the diazonium solution (which was prepared from substituted anilines, 0.375 mol; concentrated hydrochloric acid, 150 mL; water, 225 mL; and sodium nitrite, 26.3 g, in 80 mL of water) was added, and stirring continued for 30 min. Ethyl phenyl pyruvate phenylhydrazone separated as red oil, was extracted with ether, and was distilled off. The red oil obtained was dried in a vacuum over P_2O_5 and used directly for the next stage.

Dry hydrogen chloride gas was passed into a solution of the hydrazone (0.16 mol) in superdry alcohol (200 mL) with occasional shaking until the separation of ammonium chloride was complete. It was then allowed to stand for 2 h. The reaction mixture was poured into crushed ice. The separated solid was filtered, washed thoroughly with water, dried, and crystallized from absolute alcohol to obtain ethyl substituted indole-2-carboxylates (**1a–c**).

5-Substituted-3-phenylindol-2-[1,2,4-triazole-3-thione] (2a–c)

3-Phenyl-indole-2-carboxylate (0.01 mol) on reaction with thiosemicarbazide (0.01 mol) was refluxed for 8 h in 30 ml of pyridine. The solution was poured into ice/HCl. The separated solid was filtered dried and recrystallized. ^{1}H NMR data: 9.2 (s, 1H, indole NH), 8.6 (δH), 7.8 (s, triazole NH), 7.2–7.6 (Ar-H).

5-Substituted-3-phenylindol-2-[1,2,4-triazolo-3-thioacetic Acid] (3a–c)

5-Substituted-indole-2-[1,2,4-triazole-3-thione] (**2a–c**) (1 g) in acetic anhydride (10 ml) was refluxed for 3 h, then cooled and poured into water. The formed product was collected and recrystallized. ^{1}H NMR data: 9.1 (s, 1H, indole NH), 7.7 (s, 1H, triazole NH), 7.3–7.6 (Ar-H).

5-Substituted-3-phenylindole-2-thiazolo [2,3-b] Triazole (4a–c)

5-Substituted-3-phenylindole-2-[1,2,4-triazolo-3-thioacetic acid] (**3a–c**) (0.01 mol), chloroacetic acid (0.03 mol), and sodium acetate (3 g) in acetic acid (30 ml) was refluxed for 5 h, and then the solution was evaporated. The residue was washed with a little water and recrystallized. ^{1}H NMR data: 12.1 (s, 1H, indole NH), 3.3 (s, 2H, triazole CH_2), 7.3–7.6 (Ar-H).

5-Substituted-3-phenylindole-1,2,4-triazolo[3′-yl Sulfanyl Methyl] Benzimidazole (5a–c)

5-Substituted-3-phenylindole-2-[1,2,4-triazolo-3-acetic acid] (**3a–c**) (0.01 mol) and orthophenylenediamine dihydrochloride (i) (0.01 mol) in ethyleneglycol

(20 ml) was refluxed for 5 h. The reaction mixture was cooled to room temperature and poured into water (100 ml). The obtained solid was filtered and suspended in water. The pH of the solution was adjusted to 7 by the addition of sodium bicarbonate. It was filtered, washed, dried, and recrystallized. ^{1}H NMR data: 9.1 (s, 1H, indole NH), 7.8 (s, 1H, benzimidazol NH).

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